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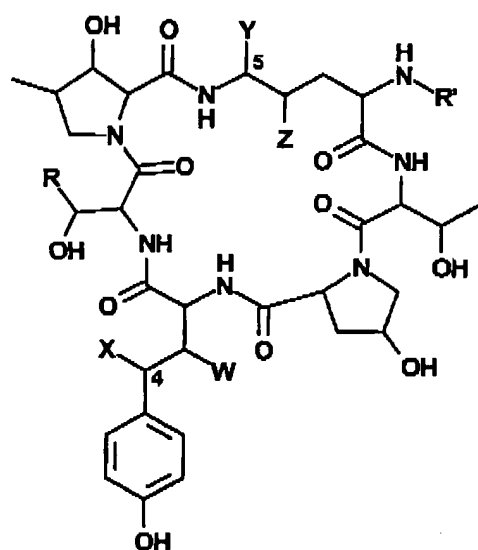
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TITLE OF THE INVENTIONA PROCESS FOR THE CONVERSION OF ECHINOCANDIN CLASS OF PEPTIDES TO
THEIR C4-HOMOTYROSINE MONODEOXY ANALOGUES

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FIELD OF THE INVENTION

This invention relates to a process for the conversion of echinocandin class of peptides of the formula I



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(I)

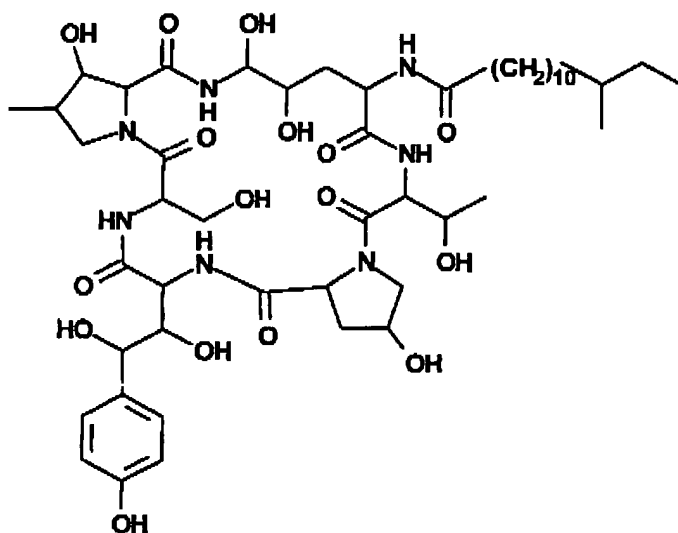
wherein W, X, Y, Z, R and R' are as defined herein below :

		<u>W</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>R'</u>
	1. Echinocandin B	OH	OH	OH	OH	CH ₃	Linoleoyl
15	2. Pneumocandin A ₀	OH	OH	OH	OH	CH ₂ -CONH ₂	10,12-Dimethyl- myristoyl
	3. Pneumocandin A ₁	H	OH	OH	OH	CH ₂ -CONH ₂	"
	4. Pneumocandin A ₂	OH	OH	H	H	CH ₂ -CONH ₂	"
	5. Pneumocandin B ₀	OH	OH	OH	OH	CH ₂ -CONH ₂	"
20	6. Pneumocandin B ₂	OH	OH	H	H	CH ₂ -CONH ₂	"
	7. Pneumocandin C ₀	OH	OH	OH	OH	CH ₂ -CONH ₂	"
	8. Mulundocandin	OH	OH	OH	OH	H	12-Methyl- t trad canoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

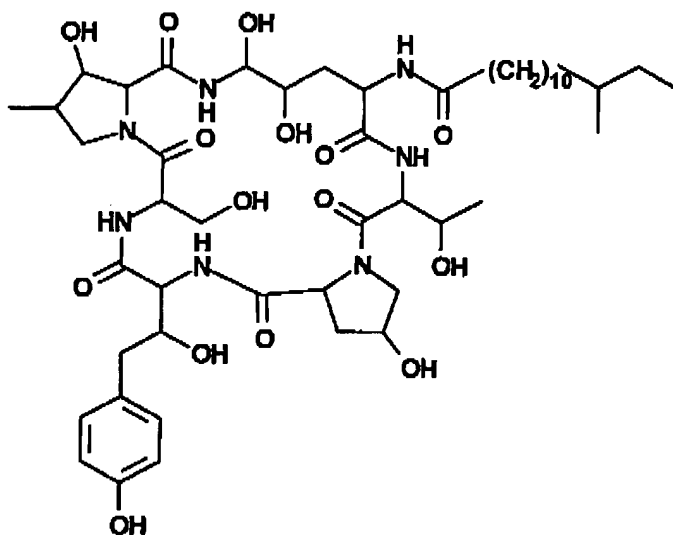
		<u>W</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>R'</u>
5	1. Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH ₃	Linoleoyl
	2. Deoxypneumocandin A ₀ OH		H	OH	OH	CH ₂ -CO-NH ₂	10,12-Dimethyl- myristoyl
10	3. Deoxypneumocandin A ₁ H		H	OH	OH	CH ₂ -CONH ₂	"
	4. Deoxypneumocandin A ₂ OH		H	H	H	CH ₂ -CONH ₂	"
	5. Deoxypneumocandin B ₀ OH		H	OH	OH	CH ₂ -CONH ₂	"
	6. Deoxypneumocandin B ₂ OH		H	H	H	CH ₂ -CONH ₂	"
	7. Deoxypneumocandin C ₀ OH		H	OH	OH	CH ₂ -CONH ₂	"
15	8. Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra- decanoyl,

particularly to a process for the conversion of mulundocandin (compound of the formula II)



(II)

to deoxymulundocandin (compound of the formula III)



(III)

BACKGROUND OF THE INVENTION

1,3- β -glucan synthesis inhibitors are effective antifungal agents against *Candida albicans* and also *Pneumocystis carini*, an opportunistic organism responsible for an often fatal pneumonitis among HIV patients and other immunocompromised hosts. Of all the structural classes of 1,3- β -glucan synthesis inhibitors, only the echinocandins received considerable attention [Ref : J. Med. Chem. 35, 198-200 (1992)]. Echinocandin class of peptides are cyclic hexapeptides having a lipophilic side chain.

Several methods for the conversion of echinocandins to the corresponding deoxy analogues under acidic conditions have been reported [Ref : Tetrahedron Letts., 33, 4529-4532 (1992); US Patent Appl. No. 222157 dated April 4, 1994]. The above methods involve selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues with prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group.

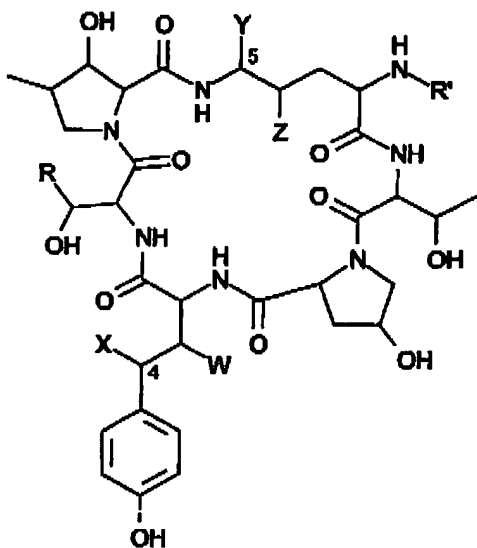
Mulundocandin [J. Antibiotics, 40, 275-280 and 281-289 (1987)] and deoxymulundocandin [Indian patent No. IN 169830 ; J. Antibiotics, 45, 618-623 (1992)] having antifungal properties were isolated from *Aspergillus sydowii* (Bainier and Sartory) Thom and Church

var. Nov. Mulundensis Roy (culture no.HIL Y-30462). Deoxymulundocandin was found to possess better antifungal activity than mulundocandin. However, the production of deoxymulundocandin during the fermentation was 200 times less than that of mulundocandin.

- 5 We have found out by extensive research and experimentation that echinocandin class of peptides of the formula I may be converted to the corresponding C4-htyr monodeoxy analogues, particularly mulundocandin to deoxymulundocandin under neutral conditions. Accordingly, the object of the present invention is to provide a process for the conversion of echinocandin class of peptides of the formula I to the
- 10 corresponding C4-homotyrosin monodeoxy analogues, particularly mulundocandin (compound of formula II) to deoxymulundocandin (compound of formula III).

SUMMARY OF THE INVENTION

- According to the invention, there is provided a process for the conversion of echinocandin class of peptides of the formula I
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wherein W, X, Y, Z, R and R' are as defined herein below :

	<u>W</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>R'</u>
1. Echinocandin B	OH	OH	OH	OH	CH ₃	Linoleoyl

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2.	Pneumocandin A ₀	OH	OH	OH	OH	CH ₂ -CO-NH ₂	10,12-Dimethyl-myristoyl
3.	Pneumocandin A ₁	H	OH	OH	OH	CH ₂ -CO-NH ₂	"
4.	Pneumocandin A ₂	OH	OH	H	H	CH ₂ -CO-NH ₂	"
5	5. Pneumocandin B ₀	OH	OH	OH	OH	CH ₂ -CO-NH ₂	"
6.	Pneumocandin B ₂	OH	OH	H	H	CH ₂ -CO-NH ₂	"
7.	Pneumocandin C ₀	OH	OH	OH	OH	CH ₂ -CO-NH ₂	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

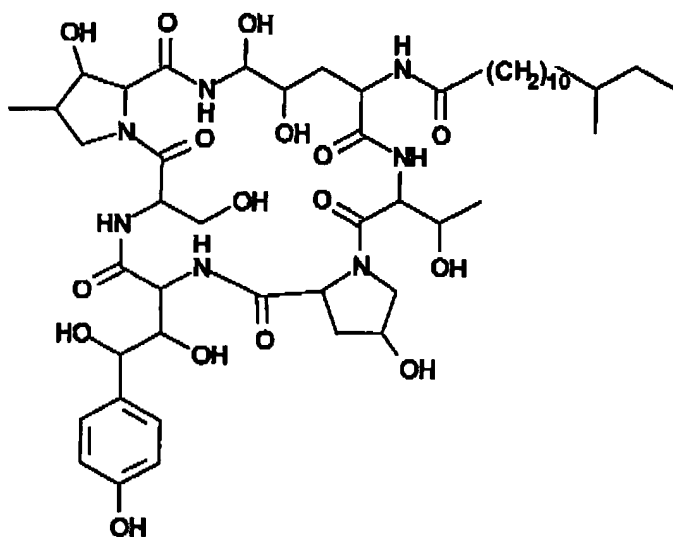
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to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

		<u>W</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>R'</u>
15	1. Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH ₃	Linoleoyl
	2. Deoxypneumocandin A ₀	OH	H	OH	OH	CH ₂ -CO-NH ₂	10,12-Dimethyl-myristoyl
	3. Deoxypneumocandin A ₁	H	H	OH	OH	CH ₂ -CO-NH ₂	"
20	4. Deoxypneumocandin A ₂	OH	H	H	H	CH ₂ -CO-NH ₂	"
	5. Deoxypneumocandin B ₀	OH	H	OH	OH	CH ₂ -CO-NH ₂	"
	6. Deoxypneumocandin B ₂	OH	H	H	H	CH ₂ -CO-NH ₂	"
	7. Deoxypneumocandin C ₀	OH	H	OH	OH	CH ₂ -CO-NH ₂	"
25	8. Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetradecanoyl

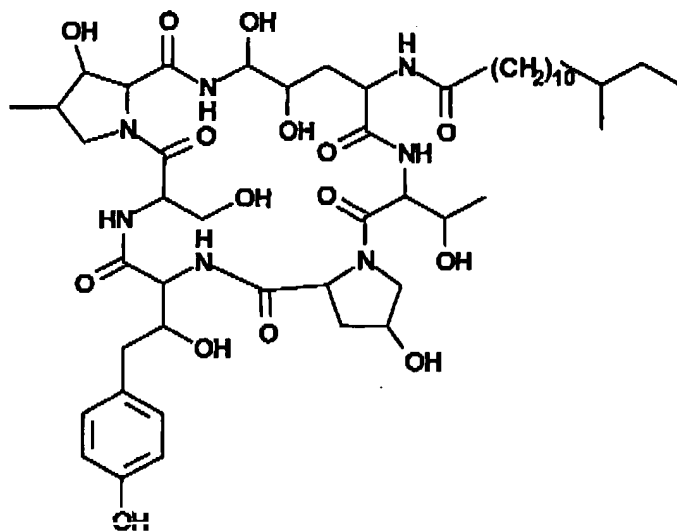
particularly to a process for the conversion of mulundocandin (compound of the formula II

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(II)

5 to deoxymulundocandin (compound of the formula III)



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which consists of a single step selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues particularly under neutral conditions without

Example 1

Mulundocandin (220 mg, 2.2 mM) in ethanol (8 ml)) was stirred with 15 ml of W-2 Raney nickel (pH 7) in ethanol (30 ml) for 3 hours at room temperature. After standing for 15 minutes the supernatant solution was decanted and Raney nickel washed with 3 x 30 ml. ethanol with stirring and filtered. Combined ethanolic solutions were concentrated by distillation under a reduced pressure of 60-70 mm/Hg at 35° C to obtain 160 mg (75%) of crude deoxymulundocandin as a slightly green solid.

The crude product was purified by liquid-liquid chromatography on ITO coil using upper layer of CH₂Cl₂ : MeOH : *n*-PrOH :H₂O as the stationary phase and the lower layer as the mobile phase in an ascending mode. The coils (15 + 25 + 215 ml) were connected in series and a flow rate of 0.6 ml/min. at a piston stroke of 60 and pressure 0.5 bars was maintained. The purification of deoxymulundocandin was monitored both by bioactivity against *Candida albicans* and *Aspergillus niger* and by analytical High Pressure Liquid Chromatography (HPLC) [column : (10 x 0.4 cm + 3 x 0.4 cm) ODS-Hypersil, 10μ; mobile phase: 50:50 CH₃CN : H₂O ; flow rate : 1 ml/min; Wavelength : 220 nm.) The fractions (4.5 ml each) containing deoxymulundocandin were combined, concentrated by distillation under a reduced pressure of 60-70 mm/Hg at 35°C and lyophilized to yield pure deoxymulundocandin [65 mg (30% yield)]. Also recovered during the above purification of deoxymulundocandin was unreacted mulundocandin in 10% yield.

The semi-synthetic deoxymulundocandin was identical in all respects to the naturally isolated compound and the physico-chemical data is given in Table 1.

TABLE 1

25	Appearance :	White powder
	Melting point :	170-172°C
	[α] _D :	- 36.6° (c 0.25, MeOH)
	HPLC RT :	4.42 min
	FAB-MS (Fast Atom:	1014.7 (M + Na) ⁺
30	Bombardment mass)	
	¹ H NMR (300 MHz, : CD ₃ OD)	Figure 1 of the accompanying drawings

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^{13}C NMR (75 MHz, : Figure 2 of the accompanying drawings
CD₃OD)

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- The chemical structure shows a macrocyclic compound with a 12-membered ring. The ring contains two amide bonds and two hydroxyl groups. Substituents include a 4-hydroxyphenyl group (labeled 4), a hydroxyl group (labeled X), a hydroxyl group (labeled W), a hydroxyl group (labeled Y), a hydroxyl group (labeled Z), a hydroxyl group (labeled R), a hydroxyl group (labeled R'), and a hydroxyl group (labeled OH).

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to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below

		<u>W</u>	<u>X</u>	<u>Y</u>	<u>Z</u>	<u>R</u>	<u>R'</u>
5	1. Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH ₃	Linoleoyl
	2. Deoxypneumocandin A ₀ OH		H	OH	OHCH ₂ -CO-NH ₂	10,12-Dimethyl-	myristoyl
	3. Deoxypneumocandin A ₁ H		H	OH	OHCH ₂ -CONH ₂	"	
10	4. Deoxypneumocandin A ₂ OH		H	H	H	CH ₂ -CONH ₂	"
	5. Deoxypneumocandin B ₀ OH		H	OH	OHCH ₂ -CONH ₂	"	
	6. Deoxypneumocandin B ₂ OH		H	H	H	CH ₂ -CONH ₂	"
	7. Deoxypneumocandin C ₀ OH		H	OH	OHCH ₂ -CONH ₂	"	
15	8. Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra- decanoyl

which consists of a single step selective reduction of C4-h Tyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues under neutral conditions without prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

2. A process as claimed in claim 1, wherein Mulundocandin is converted to Deoxymulundocandin.

3. A process as claimed in claims 1 or 2, wherein the reduction reaction is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and room temperature.

4. A process as claimed in claims 1 to 3, wherein the hydrogenolysis is carried out in the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin.